FACTORS AFFECTING THE RATE OF COOLING IN IMMERSION HYPOTHERMIA

by

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by

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INTRODUCTION

For many decades prior to the onset of the Second World War, considerable effort was put forth in the study of the physiology of heat and cold, but it was not until just a few years preceding the war that the urgency of the study was realized. Since that time many aspects of the problem arising from exposures to extremes of temperature have been investigated, adding greatly to our knowledge, yet much has been left undone. Barbour and many others (4, 10, 11, 12, 23, 24, 26, 33, 64) have reviewed the field and pointed out disputed findings and unstudied aspects of the subject.

In this thesis attention will be confined to that portion of the problem dealing with reduced body temperatures occasioned by immersion in cold water. Certain physical, physiological and chemical factors having to do with defense of the organism against hypothermia have been investigated from the standpoint of interpretation of diverse observations on the dog and albino rat during the state of hypothermia.

PHYSICAL FACTORS

EVAPORATION - Under the conditions of the present work, the effects of evaporation may be minimized. At normal body temperatures, the dog will demonstrate an evaporative heat loss from respiration and perhaps a small amount from perspiration from the pads of the feet; under conditions of immersion hypothermia, respiration is slowed, the accompanying evaporation being diminished to a minimum, and there is no chance for evaporation from the pads of the feet since they remain immersed in water throughout the period of study.

RADIATION - Deighton (24), DuBois (26), and Hardy and DuBois (40) have written comprehensive reviews in which they show that the physical factors affecting the rate of cooling and heat elimination from the body have been well correlated and that the main problem existing at present is their control. The effect of radiation on heat loss under the conditions of the present study is of little importance, since other factors can be shown to have much greater effect in immersion hypothermia.

CONDUCTION - Perhaps conduction may be considered as the predominant mechanism whereby heat is removed from the body under the conditions of immersion hypothermia. Of first importance among the many factors which affect the heat control is the skin. Swift (69, 70) has shown that subcutaneous fat by its type and distribution plays an important role in varying the conductive properties of the skin. A coat of hair or fur or clothing in humans would seem to bear an important role in varying both conduction and convection. Giaja, cited by Deighton (24), claims an increase of 78 percent in the conduction in geese and

54 percent in hens as a result of removal of feathers. Likewise, according to Forbes, cited by Deighton, the heat production of shorn cattle is increased. Ritzman and Benedict, cited by Deighton, obtained results with sheep comparable to those of Giaja with geese. Spealman (67) and Haterius and Maison (46) on the otherhand found no significant difference in the rates of cooling between normal and depilated dogs. Hardy and DuBois (40) have demonstrated that man is unable to maintain the temperature of the extremities, especially the feet which show a precipitate fall in temperature, when unclothed and mo tionless in air below 28° C. In the present work a statistical study was made on the cooling rates of dogs having different amounts of hair covering and a significant difference was observed.

CONVECTION - The effects of conduction are considerably complicated by what Deighton has called "free convection" (24). Although the animals are immersed in non-circulating water, a certain amount of convection is induced by the gravity currents set up by the warmth of the body. Of somewhat greater magnitude are the convection currents established by the rhythmical movements of shivering and respiration. The currents induced by heavy shivering could conceivably produce a marked increase in convective heat loss.

PHYSIOLOGICAL FACTORS

The most immediate protective mechanisms possessed by the body for exposure to cold are those of the circulatory system. Barcroft and Edholm (6), using a plethysmograph to measure blood flow through the arm and Spealman (66), using an indirect method of measuring blood flow through the arm, obtained comparable results for blood volume flows at similar temperatures with the rectal temperature maintained at a normal level. They found that the blood flow was at a minimum with a surrounding water temperature of 15° to 20° C. They also found the maximum flow to be obtained at a water temperature of 5° C. with high values at 10 and 25° C. The exact mechanism of the vasoconstriction has not been fully explained. Richards (62) described the descending pathways from the hypothalamus as accurately as available knowledge permitted but could not assure a reflex mechanism. Perkins, et. al. (60) found a sudden vasoconstriction in the denervated paws of cats exposed to cold and suggested that it was caused by a locally increased sensitivity to cold and a decrease in local vasodilator metabolites.

Crismon (21), using rats, found generalized severe hypothermia to have a selective unfavorable effect upon circulation as a whole. In his study, he recorded blood pressures, heart rates, and electrocardiograms and has described the typical patterns of each during the reduction of body temperature. The usual course of events during a reduction in body temperature may be described in three stages: first, a period of compensation which includes peripheral vasoconstriction and bradycardia with increased stroke volume; second, progressive circulatory

failure with continued slowing of the heart, reduced cardiac output as a result of a decreased stroke volume and arterial hypotension; third, a phase of "regional asphyxia" characterized by inhibited ventricular contraction, atrioventricular block, and signs of respiratory failure.

Circulation is further impaired by increases in blood viscosity due both to physical changes of the blood on cooling and the physiological changes in capillary size on cooling. Fahraeus and Lindquist (29) have shown marked increases in blood viscosity with reductions in capillary bore below 0.5 mm. Eckstein, Book, and Gregg (27) and Elliott (28) have demonstrated, in vitro, an increase in viscosity due to cooling.

Ariel, Bishop, and Warren (2, 3) and Talbott (71) have described circulatory changes on rewarming which deplete the subject's resistance and chances for recovery on subsequent immersions. Talbott states that restoration to a normal body temperature at a rate faster than 1.1° C. per hour produces a strain on the heart.

CHEMICAL FACTORS

A good deal of work has been done on the endocrine function in hypothermia. Many authors have attempted to compare the body state of mammals under conditions of hypothermia to that of hibernating animals. In some respects a comparison may be made, but in general a correlation is difficult to demonstrate.

Mann (57) could find no constant change in the pituitary of the spermophile on hibernation, nor could Rasmussen (61) find any weight or histological changes in the hypophysis of the woodchuck on hibernation. Cushing and Goetsch (22) on the other hand describe histological changes in the pituitaries of hibernating animals during the dormant period. They found that some of the cells of the pars anterior not only diminished in size, but also lost their typical staining properties. Tyslowitz and Astwood (72) found that hypophysectomized young rats were unable to maintain their body temperature when exposed to a cold environment. Crude pituitary extracts or purified corticotrophin increased the cold resistance of such animals. The extracts were ineffective in the absence of the adrenals but were active after thyroidectomy. Uotila (73) has offered some evidence which would indicate that the cold reaction of the thyroid is mediated through the anterior pituitary.

Mann (57) found no changes in the thyroid of the hibernating spermophile, while many authors found a definite thyroid stimulation in non-hibernating mammals exposed to cold (3, 20, 52, 55, 56, 58, 63, 68, 75). Leblond and Gross (55) have shown that the thyroid is essential as a protective mechanism against cold exposure by comparing the survival

of thyroparathyroidectomized rats exposed to an environmental temperature of 0° C. for several days to that of normals. The operated animals died within a few days, while the normals lived for several weeks. Ariel and Warren (3) and Starr and Roskelley (68) noted profound changes in the follicular epithelial height as well as changes in the follicular contents. Ariel and Warren found that in rabbits these changes, when combined with vascular engorgement, could increase the size of the thyroid from 1 1/2 to 3 times its normal size. They found that there was a tremendous increase in the circulation and a progressive increase in the epithelial height with an increasing number of vacuoles and a rapid diminution of colloid; on continued exposure, circulation is restricted as is chemical activity and exchange. Excessive exposure depletes the gland of its colloid to a state wherein it consists of large cuboidal cells and vacuoles. They also found that after partial or complete recovery from a state of hypothermia subsequent exposures would produce a hypothermic state more rapidly and more easily with a lessened chance for recovery. In such cases, the thyroid showed an abundance of colloid, which suggested to them that the gland possessed the ability of manufacturing and storing the colloid but the body was unable to utilize it, perhaps due to the failure of other mechanisms such as glucose stores.

Zarrow and Money (77) found a decreased resistance to cold in rats treated with thiouracil while Blood _et_. _al_. (7) found that thiouracil, in a dosage sufficient to reduce the oxygen consumption by 27 percent under normal conditions, did not depress the oxygen consumption significantly in the face of the stimulus of environmental cold. It

was also pointed out by this group that the metabolic stimulation of environmental cold and that of thyroxin were additive.

Many authors have found that the stimulation by cold causes a marked increase in epinephrine discharge from the adrenal medulla (14, 42, 44, 45). They have concluded that the extra output of epinephrine, by hastening combustion, serves to protect the organism against cooling. Hartman and Hartman (44) showed that the flow of epinephrine was dependent upon both the degree and area of peripheral stimulation. Other authors (8, 43, 49, 50) have demonstrated that epinephrine does actually increase the rate of heat production.

The effect of hypothermia on blood sugar levels has been extensivly investigated and the findings are closely allied with those on epinephrine and insulin. Cassidy, Dworkin, and Finney (15, 16) and Britton (9) demonstrated that a lowering of the blood sugar concentration by means of insulin causes a fall in body temperature which is not accompanied by shivering. When these hypoglycemic animals are immersed in cold water they do not shiver at once, but concurrent with a rise of the blood sugar level to normal or to a hyperglycemic level shivering commences. The shivering reflex can be abolished by the administration of insulin but may be caused to reappear upon the administration of dioxyacetone, fructose, mannose, galactose, glucose, epinephrine, or pituitrin (16). Fasting was found to improve the resistance to hypothermia in rats (32). Fuhrman and Crismon also found that blood glucose rose in rats having ample carbohydrate stores but fell in fasted or slowly cooled animals. Cori and Cori (17-19) have offered an explanation

for this phenomena by proving that circulating epinephrine induces the utilization of muscle glycogen and not that of the blood sugar. Thus the epinephrine released on cold stimulation would cause a rise in blood sugar levels provided there were ample carbohydrate stores in the muscle.

One of the most variable and least understood mechanisms for protection against exposure to cold is that of shivering and increased muscular tone. The work of Uprus, Gaylor, and Carmichael (74) correlating rectal temperature changes to shivering responses upon immersion of human subjects in warm and cold baths and the work of Hemingway (47), which followed shivering responses to diathermy treatment in dogs, lend support to the contention that shivering is caused by a central stimulation at the hypothalamus. On the other hand, the observations of Jung, Doupe, and Carmichael (51), following the shivering responses of human subjects exposed to cold drafts of air, as well as the observations of Penrod (59) on the cessation of the shivering responses of the rewarming dogs suddenly immersed in a warm bath lend support to the contention that the stimulus for shivering is of peripheral origin.

Although Haterius and Maison (46) felt that shivering exerted no marked influence upon the rate of cooling, Swift (69), Hardy and Goodell (41), Penrod (59), and Barbour _et_. _al_. (5) have demonstrated an increased metabolism in dogs, rats, and humans with the onset of shivering. Penrod (59) found the shivering to be intense enough in one animal to reverse the fall in rectal temperature for a brief period of time even with the dog immersed in water of 3° C. Woodruff (76), using nembutalized dogs, showed that shivering would stop the cooling

until more anesthetic had been administered. Finney, Dworkin, and Cassidy (31) have reported that the occurrence of shivering is associated with a rise in the respiratory quotient and vice versa. Spealman (66) and Burton and Bronk (13) report 35 to 37° C. to be a critical core temperature for the onset of shivering. Swift (69, 70), on the other hand, believes that there need be no fall in rectal temperature whatsoever in order to stimulate shivering but that a skin temperature of 19° C. is the necessary stimulus in humans.

Many authors have also reported that a detectable shiver was not always necessarily present with an increased metabolic rate (13, 54, 70). This increase in metabolic rate could only be ascribed to an increase in muscular tone.

OTHER FACTORS

Age has some effect on the rate of cooling in that very young rats were reported to be poikliothermic by Fairfield (30). Hill (48) reports 5 periods in the life span of the rat with an increasing resistance to cooling from birth to a maximum between 61 and 300 days which is then followed by a period of slow deterioration in the cold resisting mechanism.

Oxygen tension apparently has an effect on the rate of cooling, for Kottke et. al. (53) have reported a delay in the onset of shivering under conditions of high oxygen tension. Gellhorn and Janus (34, 35) have also reported that a lowered oxygen tension results in a fall in body temperature, while a lowered barometric pressure with a normal partial pressure of oxygen has no effect. Grossman and Penrod (38) have also reported that oxygen tensions in the order of 5.2 and 5.8 atmospheres cause a fall in rectal temperatures in rats when the body temperatures are normal and a rise when the rectal temperature is at 20° or 25° C. They also found an oxygen tension of 5.2 atmospheres to be protective at a rectal temperature of 20° C., but to be detrimental at a rectal temperature of 25° C. This protection at 20° C. could be explained on the basis of the lowered metabolic activity shown to exist at that temperature. This contention is given further support in another study by the same authors (37) in which it was found that thiouracil treated rats were significantly protected against high oxygen toxicity. The converse was also found to be true, i.e., that at 25° C., at which temperature metabolism was at a maximum, the high oxygen

tension exerted its most toxic effect and thyroxin treated rats were more susceptible to high oxygen toxicity.

In experimental hypothermia variations in the type of anesthetic and the degree of anesthesia have a profound effect upon the rate of cooling. The choice of a proper anesthetic, where one is required, has proved to be a stumbling block to many experiments. The use of the long acting anesthetics seems ill-advised since the cold itself will act as an anesthetic below a temperature near 27° C. The short acting barbiturate, pentothal sodium, was the anesthetic of choice in our laboratory under most conditions. It might seem that the volatile anesthetics would be more effective since they can be rapidly blown off, but Haterius and Maison (46) found animals administered cyclopropane to behave identical to those administered pentothal. The fact that an anesthetic has a profound effect on the rate of cooling can be attested by the observations of Woodruff (76) that, when very light, his animals would stop cooling until a further administration of nembutal was effected. Spealman (67) also observed that large dogs would not cool in water at 20° C. or above unless an anesthetic were administered.

A discrepancy also exists in the literature in the type of cooling used. Our method of cooling, that of submersion in ice water, seems to be the most severe. The method of cooling in a water jacket seems to be slightly less severe, while that of cooling in a refrigerator or coil seems to be least severe. Thus, it can be seen that the method of cooling must be taken into consideration when comparing data on hypothermic animals reported from different laboratories.

In the following pages of this thesis we will be concerned mainly with the physical effect of hair coat and the chemical effect of thyroid and to some extent epinephrine upon the rate of cooling in the dog. Consideration will also be given to the effects of shivering, body size, and anesthetic. Wherever possible an analysis of the data will be made in such a manner that only one factor could possibly exert an influence upon the cooling rate, but due to the complexity of the combination of factors a certain amount of overlap cannot be avoided.

METHODS

Observations for the work to be reported in this thesis were made on dogs and on albino rats. In general the dogs were unselected and of healthy stock. Concurrent observations of a varied nature were made on many of the dogs, but in general they were all prepared in a similar manner. In all cases a preliminary sedative dose of pentothal sodium was administered per venam. In circumstances under which surgery was to be performed, the necessary level of anesthesia was obtained either with additional dosage of pentothal sodium or with ether. The animals were strapped in a supine position on a dog board, an endotracheal tube inserted and, if the experiment demanded it, the oxygen consumption of the anesthetized dog was determined using a Sanborn closed circuit respirometer. Subsequent to the oxygen consumption determination, if no surgery were in order, the dogs were immersed to the mid thoracic region in a bath tub of ice water, leaving the anterior thorax, neck and head exposed to the air. The temperature of the bath ranged from 2° to 5° C.

Temperatures were recorded on a Leeds Northrup Speedomax from thermocouples which had been inserted into various parts of the body. Rectal temperatures were recorded in all of the experiments, the thermocouple being inserted approximately four inches into the rectum and then rotated until it could no longer be palpated from the ventral surface. Occasionally mediastinal, liver, brain, and heart temperatures were recorded. The heart temperature was obtained from a thermocouple catheter inserted into the right heart via the jugular vein. The exact position of the thermocouple was determined at autopsy and was located

in either the right atrium or ventricle. Graphs plotting deviations of heart, brain, mediastinal, and liver temperatures from that of the rectum were prepared in the laboratory for use in predicting other temperatures when only the rectal temperature was recorded.

Although there has been some doubt concerning the significance of the rectal temperature as being representative of the temperature state of the remainder of the body, a reliable record of the fall in visceral temperature may be obtained if proper care is taken in the placement of the rectal thermocouple.

In order to standardize the shivering intensity, an arbitrary scale was established. The scale, 0 to 4, graded the intensity according to degree of muscular involvement, slight tremors in the head, neck, and shoulders being graded as 1; regular and rhythmical tremors in the head, neck, forelegs, and trunk being graded as 2; general muscular twitching throughout the body being graded as 3; and severe movement being graded as 4. In the analysis of the data obtained, the shivering intensity was graded in accordance with the time and type of muscular involvement, the same arbitrary scale being used, and, in most instances, by the same observers.

If the dogs were to be revived, they were cooled to a rectal temperature of 20° C. or until respiration ceased, whichever being higher, at which time they were removed from the cold water and immersed in a warm bath, 41° C., for 30 minutes. If the animals were to be sacrificed, they were cooled until the heart beat could no longer be detected.

The surgery consisted most often of a neck incision with a

through and through carotid cannulation and a jugular catheterization. Occasionally, when the brain temperature was to be recorded, a skin flap was retracted from the skull and a hole drilled in the temporal part of the frontal bone a few centimeters from the parietal crest and just in front of the parietal bone, occasionally the rostral portion of the parietal bone was drilled. In a few instances, when the neck operation was not performed, a femoral cannulation for blood pressure determination was made. At the completion of the surgery, the animal was immersed in the prescribed manner and cooled to cessation of the heart beat.

The immersion period required to achieve a rectal temperature of 20° C. varied from 52 to 227 minutes (average 126). The mean rate of cooling to 20° C. was computed for each animal from the "Speedomax" temperature recordings.

In several instances subsequent immersions were effected in a manner similar to that described above. For statistical evaluation of the results from such experiments the paired data method was used, while for all other analyses statistical tests were by the method of random group comparisons or the analysis of variance.

In the experiments in which thyroid stimulation was required, the dogs were fed a diet containing 4 mgm USP thyroid[1] per kilogram body weight daily for 13 days after they had been twice cooled to 20° C. and rewarmed.

The dogs studied in the depilation experiments were prepared after one immersion in the ice water. The animals were clipped closely

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[1] Armour, 1/4 grain tablets, Armour & Co., Chicago, Ill.

using small animal clippers. All hair was removed from the body and legs, but was not removed from those parts of the body which were not to be immersed in water, the face, cranium, and upper dorsal neck region. A seven to eight day rest period between immersions was observed in both the thyroid and depilation experiments.

Male albino rats of approximately 200 grams body weight were used in one set of experiments. They were divided into two series. The first series consisted of 90 rats divided into three groups, a hyperthyroid group, a hypothyroid group, and a control group. Each group was further divided into six units of five rats each, assembled in such a manner that the weight of a control unit was compared to that of a hyperthyroid and a hypothyroid unit. The hyperthyroid group was maintained on a stock Rockland Farms diet to which 0.12% USP thyroid[1] was added for nine days prior to immersion. The hypothyroid group was maintained on the same diet to which 0.03% 6-n-propyl-thiouracil[2] was added for 24 days prior to immersion. Three of these rats died prior to the immersion. At the end of the diet period, the rats were fasted for 24 hours and the oxygen consumption along with that of the controls was measured using a closed circuit system which consisted of a large bell jar seated in a ring of mercury and attached to a Sanborn respirometer. (See Figure 1.)

Fifteen rats, five of each group, were then placed in tight fitting boxes, which were so constructed that the tail could be held outside the box while a rectal thermometer was inserted. The rats were immersed

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1. Powder No. 58, Eli Lilly & Co., Indianapolis, Ind.
2. Kindly furnished by Lederle Laboratories.

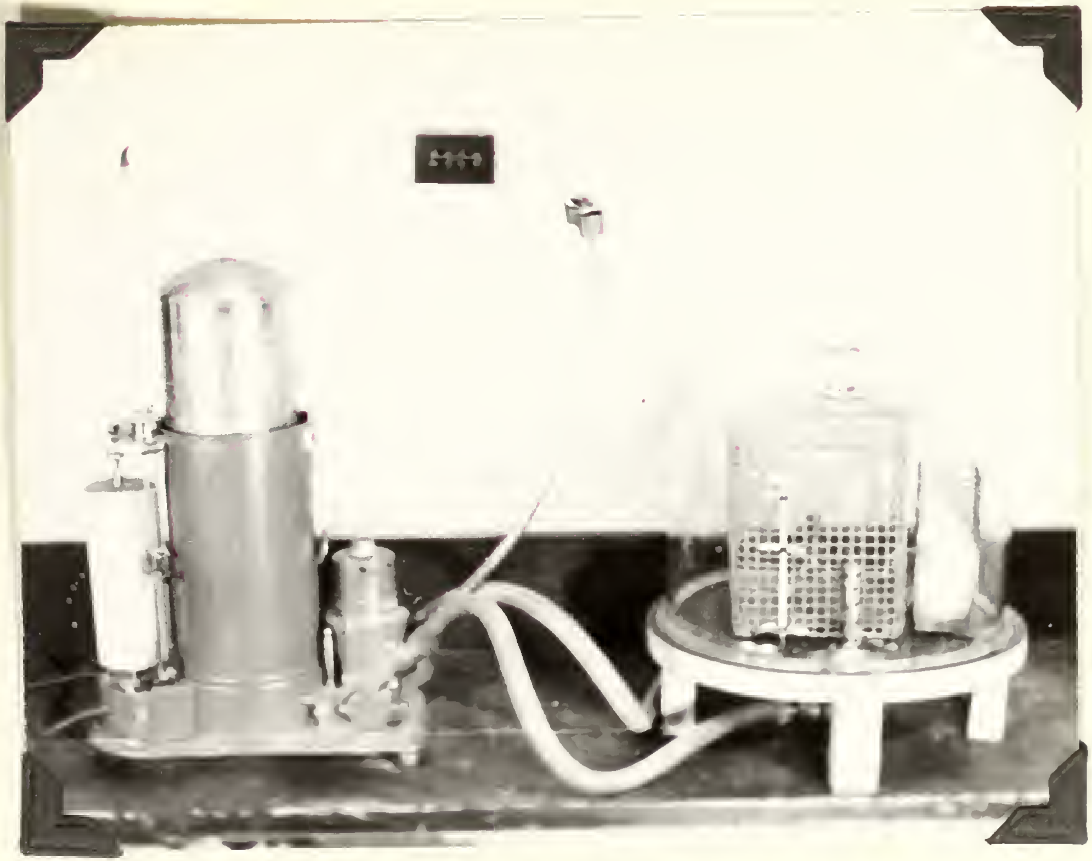

Figure 1. Apparatus for determining oxygen consumption of albino rats.

simultaneously to the shoulders in an ice bath maintained at 7° C. Rectal temperatures, prior to and periodically during immersion, were determined using a laboratory thermometer inserted approximately 4 cm. into the rectum. The rats were cooled to a rectal temperature of 15.8 to 16.0° C., and then removed from the ice bath and rewarmed in air at room temperature, the time of cooling being recorded. The animals were observed for one week postexperimentally at which time survivors were counted.

The second series was prepared in a similar manner, but the thyroid diet was increased to 0.50% and maintained for 15 days, while the 6-n-propyl-thiouracil diet was kept at 0.03% but was maintained for 30 days. The rats of the second series were cooled to a rectal temperature of 14.8 to 15.0° C.

RESULTS

The data obtained from the immersion of the two series of albino rats is presented in Tables 1 and 2. The mean oxygen consumption in mg./100 gm. rat/ hour, the mean cooling times to 15.8-16.0° C. in the first series and to 14.8-15.0° C. in the second series, and the survivors for hypothyroid, control, and hyperthyroid rats are tabulated for each series. A statistical test comparing the cooling times of the hypothyroid rats to the cooling times of the controls shows a significant difference to exist, the hypothyroid rats cooling more rapidly than the controls. All pertinent data concerning the immersion of the thyroxin treated dogs is presented in Table 3, dog numbers G-1 to G-15 inclusive. The mean cooling rate on first immersion for dogs G-1 to G-6 is 0.173±0.0555° C/min and the oxygen consumption was 0.428±0.0385 l/kgm./hour while on second immersion the cooling rate decreased to 0.150±0.0478 ° C./min. and the oxygen consumption increased to 0.455±0.0470 l/kgm./hr., neither change being statistically significant. On a third immersion, after the dogs had been fed a 4 mgm./kgm. thyroxin diet for 13 days, the rate of cooling had increased significantly to 0.243±0.0269 ° C./min. without an appreciable change in oxygen consumption, 0.441±0.0688 l/kgm/hr. The numbers in parenthesis after dogs G-7 to G-15 refer to the original G-series number. Dog G-4 died on recovery from the first immersion and G-2 on recovery from the second.

A complete listing of the data for all of the other dogs studied for the preparation of this thesis is presented in Table 3. The C-series dogs were prepared with a neck operation consisting of a carotid

Table 1. Survival, O_2 consumption, and time of cooling to 15.8-16.0° C. of hypothyroid, control, and hyperthyroid albino rats.

HYPOTHYROID[1]			CONTROL			HYPERTHYROID[2]		
O_2 Consumption mg./100 gm. rat/hr.	Avg. Cooling Time[3] Min.	Survivors	O_2 Consumption mg./100 gm. rat/hr.	Avg. Cooling Time[3] Min.	Survivors	O_2 Consumption mg./100 gm. rat/hr.	Avg. Cooling Time[3] Min.	Survivors
145	31	3 of 4	172	41	4 of 4	188	52	5 of 5
93	39	5 of 5	119	48	4 of 4	137	39	5 of 5
126	29	3 of 5	141	35	5 of 5	140	35	3 of 5
111	29	2 of 5	154	33	3 of 5	170	31	2 of 5
110	37	2 of 5	118	41	3 of 5	146	36	1 of 5
129	31	5 of 5	141	40	2 of 5	177	43	3 of 5
Mean 119±18.2	Mean 33±6.1	Total (69%)	Mean 141±20.8	Mean 39±8.5	Total (75%)	Mean 160±21.5	Mean 40±9.5	Total (63%)

1. 0.03% 6-n-propylthiouracil for 24 days.
2. 0.12% desiccated thyroid for 9 days.
3. Bath temperature 7± 2° C.

Table 2. Survival, O_2 consumption, and time of cooling to 14.8-15.0° C. of hypothyroid, control, and hyperthyroid albino rats.

HYPOTHYROID[1]			CONTROL			HYPERTHYROID[2]		
O_2 Consumption mg./100 gm. rat/hr.	Avg. Cooling Time[3] Min.	Survivors	O_2 Consumption mg./100 gm. rat/hr.	Avg. Cooling Time[3] Min.	Survivors	O_2 Consumption mg./100 gm. rat/hr.	Avg. Cooling Time[3] Min.	Survivors
122	19	1 of 5	181	29	3 of 5	222	30	3 of 3
134	22	2 of 5	156	25	4 of 5	215	19	1 of 3
119	24	1 of 5	145	27	0 of 5	234	26	1 of 5
157	20	5 of 5	156	28	3 of 5	231	25	1 of 5
Mean 133±17.3	Mean 21±4.4	Total (45%)	Mean 160±15.3	Mean 27±5.7	Total (50%)	Mean 226±8.7	Mean 25±5.8	Total (38%)

1. 0.03% 6-n-propylthiouracil for 30 days.
2. 0.50% desiccated thyroid for 15 days.
3. Bath temperature 7±2° C.

Table 3. Laboratory data for cooling of dogs to a rectal temperature of 20° C.

Dog No.	Weight (kg.)	Mean Rate of Cooling °C/Min.	Initial Temp. °C.	Anes-thetic[1]	Rx[2]	Hair Cover	Shiver Grade	Sex	Oxygen Consump-tion l/kg/hr
C-1	8.6	.133	39.6	P	S	long	3	F	
C-2	6.9	.089	40.5	P	S	long	3	F	
C-3	13.3	.123	39.7	P	S	long	4	F	
C-4	11.4	.105	37.9	P	S	long	3	M	
C-5	9.5	.187	39.8	P	S	short	0	M	
C-6	13.2	.126	39.6	P	S	short	3	F	
C-7	7.7	.151	39.6	P	S	long	2	F	
C-8	8.3	.101	38.1	P	S	long	3	F	
C-9	10.8	.150	39.1	P	S	short	3	M	
C-10	9.3	.146	38.2	P	S	long	3	F	
C-11	21.2	.102	39.2	P	S	long	2	M	
C-12	11.2	.157	38.5	P	S	short	1	M	
C-14	7.8	.214	39.0	P	S	short	0	M	
C-15	15.3	.128	39.1	P	S	long	2	F	
C-25	7.0	.173	39.0	P	S	short	0	F	
C-26	9.4	.098	39.3	P	S	long	2	F	
C-27	7.0	.133	39.3	P	S	long	1	F	
C-28	6.8	.147	37.4	P	S	short	0	F	
C-29	16.7	.094	39.8	P	S	long	1	M	
C-30	12.8	.151	38.4	P	S	short	3	F	
C-31	8.4	.209	39.0	P	S	short	1	M	
C-32	16.7	.099	39.5	P	S	long	4	M	
C-33	11.0	.098	40.1	P	S	long	0	M	
C-34	10.5	.171	39.0	P	S	short	0	F	
C-35	16.2	.174	38.8	P	S	short	2	F	
C-36	16.0	.173	38.9	P	S	short	2	M	
C-37	8.0	.171	37.8	P	S	short	2	F	
C-38	9.9	.167	39.0	P	S	long	0	M	
C-39	18.5	.148	38.3	P	S	short	2	F	
E-1	14.3	.106	39.4	P	S	short	4	M	
E-2	10.9	.136	39.7	P	S	long	3	M	
E-3	8.4	.189	38.5	P	S	short	1	F	
E-4	5.8	.143	39.1	P	S	short	0	F	
E-5	8.3	.100	38.8	P	S	long	3	F	
E-6	10.9	.146	38.7	P	S	long	2	F	
E-7	13.0	.101	36.8	P	S	long	1	M	
E-8	18.8	.112	40.3	P	S	long	1	M	
E-9	10.3	.148	39.0	P	S	short	1	M	

1. P equals pentothal; E equals ether.
2. S equals surgery; NS equals non-surgery.

Table 3. (continued)

Dog No.	Weight (kg.)	Mean Rate of Cooling °C/Min.	Initial Temp. °C.	Anesthetic[1]	R_x[2]	Hair Cover	Shiver Grade	Sex	Oxygen Consumption l/kg/hr
E-10	16.0	.123	38.8	P	S	short	2	M	
E-11	11.0	.180	39.2	P	S	short	2	F	
E-12	14.5	.103	39.0	P	S	long	1	M	
E-13	18.1	.117	38.5	P	S	short	1	F	
A-1	9.5	.259	38.8	P	NS	short	3	M	.414
A-2	13.6	.256	39.2	P	NS	short	1	M	.378
A-3	15.6	.367	38.5	P	NS	short	1	F	.300
A-4	14.0	.158	39.7	P	NS	long	3	M	.372
A-5	20.4	.218	40.1	P	NS	short	0	M	.336
A-6	15.6	.120	39.7	P	NS	long	4	M	.284
A-7	10.7	.276	39.9	P	NS	long	1	F	.504
A-8	7.9	.320	38.9	P	NS	short	1	M	.378
A-9	14.0	.363	39.9	P	NS	short	1	M	.438
A-10	14.0	.272	40.0	P	NS	short	1	F	.360
A-11	12.8	.156	39.8	P	NS	long	4	M	.348
A-12	20.8	.229	39.5	P	NS	short	0	M	.384
A-13	15.1	.122	38.8	P	NS	long	4	M	.300
A-14	9.5	.338	38.9	P	NS	long	1	F	.426
G-1	14.6	.239	39.1	P	NS	short	3	M	.414
G-2	16.0	.095	38.3	P	NS	long	2	M	.365
G-3	11.7	.195	38.1	P	NS	short	4	M	.422
G-4	17.8	.114	38.0	P	NS	short	4	F	.453
G-5	8.0	.196	38.6	P	NS	short	1	M	.442
G-6	18.5	.196	38.2	P	NS	short	1	M	.474
G-7(2)	16.1	.091	38.8	P	NS	long	3	M	.388
G-8(1)	16.1	.160	37.6	P	NS	short	2	M	.514
G-9(3)	11.1	.124	36.5	P	NS	short	3	M	.460
G-10(5)	7.6	.154	37.1	P	NS	short	0	M	.435
G-11(6)	18.4	.220	38.0	P	NS	short	2	M	.476
G-12#(1)	14.0	.212	38.2	P	NS	short	4	M	.428
G-13#(3)	9.6	.272	37.4	P	NS	short	2	M	.432
G-14#(6)	16.7	.258	38.3	P	NS	short	0	M	.368
G-15#(5)	6.3	.231	37.1	P	NS	short	2	M	.534
K-1	7.5	.212	37.8	P	NS	short	0	F	
K-2	13.1	.134	39.9	P	NS	long	1	M	
K-3	11.5	.120	38.2	P	NS	long	1	M	
K-4	11.6	.193	41.0	P	NS	short	2	M	
K-5	14.4	.125	39.3	P	NS	long	2	F	
K-6	19.4	.097	39.5	P	NS	short	2	M	
K-7(1)	7.4	.198	39.2	P	NS	none	3	F	
K-8(2)	11.5	.167	40.0	P	NS	none	1	M	

# Maintained on a 4 mgm/kg thyroxin diet for 13 days prior to immersion.

Table 3. (continued)

Dog No.	Weight (kg.)	Mean Rate of Cooling °C/Min.	Initial Temp. °C.	Anesthetic[1]	R_x[2]	Hair Cover	Shiver Grade	Sex	Oxygen Consumption l/kg/hr
K-9(3)	9.6	.269	37.2	P	NS	none	0	M	
K-10(5)	12.5	.188	39.9	P	NS	none	1	F	
K-11(6)	19.4	.186	38.6	P	NS	none	0	M	
K-12(1)	6.5	.201	38.9	P	S	none	2	F	
K-13(3)	11.3	.224	38.4	P	S	none	0	M	
K-14(5)	12.0	.157	39.1	P	S	none	0	F	
K-15(6)	19.4	.105	38.5	P	S	none	3	M	
K-16	13.1	.125	38.8	P	S	long	3	F	
K-17	7.9	.166	38.4	P	S	long	0	F	
K-19	27.5	.115	39.0	P	S	short	3	M	
K-20	27.0	.200	37.6	P	S	short	3	M	
D-42	8.8	.113	38.5	E	S	long	1	M	
D-43	8.2	.095	39.5	E	S	long	2	M	
D-45	12.8	.086	38.6	E	S	short	4	M	
D-46	11.0	.096	38.4	E	S	short	0	M	
D-52	11.2	.136	37.6	E	S	short	1	F	
D-54	10.3	.145	38.1	E	S	short	3	F	
D-55	9.5	.139	37.8	E	S	long	3	M	
D-56	16.9	.130	37.1	E	S	short	2	M	

cannulation and right heart catheterization, via the right jugular vein. The E-series dogs were prepared with a femoral cannulation, the brain operation previously described, and occasionally with a right heart catheterization. No surgery was performed on the A-series dogs, only oxygen consumption and rate of cooling observations being made. Dogs K-1 to K-6 were cooled with no treatment other than pentothal anesthetization; K-7 to K-11 were depilated prior to immersion and were the same dogs as K-1 to K-6, the numbers in parenthesis referring to the original K number; K-12 to K-15 were also depilated but the carotid cannulation, jugular catheterization and brain operation had also been performed on them prior to immersion. Dog K-4 died on recovery from the first immersion and dog K-2 died on recovery from the second immersion. Dogs K-16 to K-20 were prepared with the neck and brain operations; D-42 to D-56 were the only dogs anesthetized with ether, an initial injection of pentothal having been administered, and a neck operation consisting of a right carotid cannulation, left carotid catheterization, and a right jugular catheterization.

For a statistical analysis, the animals were broken down to numerous groups and sub-groups. A summary of this grouping with corresponding mean cooling rates, in red type, for each group and sub-group is presented in Tables 4 and 5. The number in parenthesis indicates the number of dogs in that particular sub-group. In the case of the weight sub-groups and the graded shivering intensity sub-groups, a combined mean rate of cooling was computed for a statistical analysis since it did not seem that any one group would influence the combined mean to any

great extent.

The most pertinent statistical results are tabulated in Table 6.

Table 4. Summary of analyzed data for graded shivering intensity, mean rates of cooling in °C./Min. (Number in parenthesis referring to the number of animals used.)

SUB-GROUP	GRADED SHIVERING INTENSITY				
	0	1	2	3	4
Non-surgery Long Hair		0.217 ±0.1072 (4)	0.110 ±0.0212 (2)	0.125 ±0.0475 (2)	0.133 ±0.0145 (3)
Non-Surgery Short Hair	0.203 ±0.0336 (4)	0.281 ±0.0719 (7)	0.168 ±0.0532 (4)	0.207 ±0.0730 (3)	0.154 ±0.0574 (2)
Surgery Long Hair	0.144 ±0.0396 (3)	0.109 ±0.0150 (5)	0.125 ±0.0244 (5)	0.117 ±0.0207 (8)	0.111 ±0.0170 (2)
Surgery Short Hair	0.173 ±0.0264 (6)	0.164 ±0.0360 (5)	0.162 ±0.0219 (6)	0.148 ±0.0328 (5)	0.106 ±00000 (1)
Combined Results	0.175 ±0.0368 (13)	0.200 ±0.0915 (21)	0.146 ±0.0369 (17)	0.142 ±0.0478 (18)	0.129 ±0.0314 (8)

Table 5. Summary of the analyzed data.

- Non-surgery 0.197±0.0804 (31)
  - Long Hair 0.158±0.0779 (11)
    - 0 to 9.9 Kg. 0.338 (1)
    - 10.0 to 14.9 Kg. 0.162±0.0584 (6)
    - 15.0 Kg. & above 0.107±0.0172 (4)
  - Short Hair 0.219±0.0739 (20)
    - 0 to 9.9 Kg. 0.228±0.0635 (5)
    - 10.0 to 14.9 Kg. 0.235±0.0740 (7)
    - 15.0 Kg. & above 0.200±0.0837 (8)
  - Depilated 0.202±0.0392 (5)

- Surgery 0.140±0.0335 (46)
  - Long Hair 0.120±0.0238 (23)
    - 0 to 9.9 Kg. 0.128±0.0295 (10)
    - 10.0 to 14.9 Kg. 0.117±0.0180 (8)
    - 15.0 Kg. & above 0.107±0.0135 (5)
  - Short Hair 0.160±0.0301 (23)
    - 0 to 9.9 Kg. 0.179±0.0260 (8)
    - 10.0 to 14.9 Kg. 0.149±0.0236 (8)
    - 15.0 Kg. & above 0.150±0.0334 (7)
  - Depilated 0.172±0.0525 (4)

Male long hair surgery
0.112±0.0227
(10)

vs.

Female long hair surgery
0.126±0.0235
(13)

Pentothal surgery
0.140±0.0335
(46)

vs.

Ether surgery
0.118±0.0230
(8)

Table 6. Results of statistical tests for rates of cooling in the dog.

	"t"	"F"	P
1. Reduced by surgery	4.318	-----	<0.001
2. Reduced by increasing amounts of hair (Short to long hair)			
a) Non-surgery	2.148	-----	0.043
b) Surgery	5.000	-----	<0.001
3. Reduced by increased shiver intensity (Combined figures)	-----	3.802	<0.01
4. Increased by thyroid stimulation	3.667	-----	<0.01
5. Reduced by ether anesthetic as compared to pentothal	1.774	-----	>0.05
6. Reduced by increasing body weight (Combined figures)	-----	0.857	>0.05

DISCUSSION

That the thyroid is a functional mechanism in the protection from exposure to cold has been fairly well established by the work of Leblond and Gross (55) who showed a lowered survival in thyroparathyroidectomized rats as compared to controls and also by Dempsey and Astwood (25) who showed that under concurrent antithyroid and thyroxin administration, the rat required 5.2 micrograms of thyroxin daily for maintenance of a normal thyroid, while at 1° C. the rat required 9.5 micrograms of thyroxin per day. The results of the work presented in this thesis would seem to indicate, as does the work of the above authors, that a normally functioning thyroid is essential for a maximum protection on exposure to cold. The results also indicate that the normally functioning thyroid offers a maximum of protection, which cannot be enhanced with a further administration of the thyroid hormone. It would seem, therefore, that under normal environmental conditions the thyroid is not functioning at its capacity, but is capable, under severe stress, of supplying the increased demands of the tissues for the hormone.

Actually, an interpretation of the data obtained in both the experiments of thyroid stimulation on rats and those on dogs could lead to the conclusion that thyroxin is contraindicated for acute cold exposure. It will be noted that although the metabolism of the dogs was not increased on thyroxin treatment, the rate of cooling did increase significantly. It will also be noted in the case of the rats fed on a 0.5% thyroxin diet that the mean cooling rate was increased over that of the controls although it was not statistically significant. The results obtained with the 0.12%

thyroxin diet do not follow those for the 0.5% diet, but the 0.12% diet did not stimulate the metabolism significantly whereas the higher diet did.

A difference exists between control metabolism and mean cooling time for the two series and can only be explained on the basis of an age difference. The rats used in the first series of experiments were approximately 6 months old, while those used in the second series were less than 3 months old.

A correlation between the metabolic state and the time of cooling may exist. A positive correlation of 0.94 was obtained in testing the first series of rats, but one of only plus 0.45 was found for the second series. The positive correlation of 0.94 approaches, but is not, significant, whereas that of 0.45 is far from the level of significance. It was observed, however, that several of the thyroxin treated rats in the second series died previous to the immersion in the cold bath. This might indicate that the thyroid diet had approached the toxic level for the particular strain of rat used in the experiment. If so, the mean cooling time observed for these rats is not a real value and should not be considered.

Whether the decreased cooling time observed in the second series of rats was due to the toxicity of the thyroxin diet or due to some detrimental effect of the hormone on cold exposure cannot be determined without further study but a certain amount of favor must be given to the latter hypothesis in view of the results obtained with the thyroxin treated dogs. In any case, it would appear that the effects of the

hormone do not warrant its use as a protective measure.

Aside from the possible indication that a high thyroid diet will cause an increase in the rate of cooling, there is an indication that such a diet will lower the chances for recovery from immersion hypothermia. A survival lower than that found in either controls or thiouracil treated rats was found to exist for both series of rats tested. The lowered survival was not significant but was consistent, being 12% less than that of controls and 6-7% lower than that of the thiouracil treated animals.

It is of interest to note that the thyroid of the dog does not respond in a normal fashion to thyroxin administration. The thyroxin dose administered under the conditions of this experiment was computed on the basis of the dose required to increase human metabolic rate by 30%. This dose was doubtless insufficient and must be increased many fold before an observable stimulation can be obtained. Gerard and McIntyre (36) obtain a 25% increase in metabolic rate in dogs using 0.6 grams per kilogram per day for 3-6 weeks. Due to this idiosyncracy of the thyroid in dogs, it seems inadvisable to use them in the study of thyroid function.

The LD_{50} for the rats cooled in a water bath of 7° C. found in this work to be 14.8-15.0° C. is in close agreement with that found by Adolph (1) when the bath temperature was maintained at 14.8° C. It is also in rough agreement with the values found by Hamilton (39) who cooled unanesthetized rats by immobilization in cold air.

The permanent effect of immersion on the thyroid, if there should

be any, is questionable. Ariel et. al. (2,3) found that a second immersion of the rabbit produces a hypothermic state more easily and more rapidly, but the thyroid showed an abundance of colloid. Penrod (59) could find no significant increase in oxygen consumption in the dogs on a second immersion, nor could he find a significant increase in the rate of cooling although there was a trend in each instance.

Perhaps the most enlightening finding in this work was that of the effect of surgery upon the rate of cooling. A mean cooling rate of 0.197±0.0804° C./min. was found to exist for those dogs upon which there had been no surgery performed, while a mean rate of 0.140±0.0335° C./min. was found to exist for those animals upon which surgical procedures had been carried out. By expressing these rates of cooling as the time of cooling from a normal body temperature of 39° C. to a sub-normal temperature of 20° C., it would be found that it took the non-surgery dogs an average of 96.4 minutes to cool while it took the surgery dogs an average of 135.7 minutes to cool. Subjecting these values to a "t" test, a value of 4.318 was obtained which indicates a high degree of probability (P is less than 0.001) that the surgical procedures do effect a slowing in the rate of cooling. The only apparent explanation for this effect is that of the release of epinephrine upon the application of surgical procedures. The fact that surgical operations do increase the output of epinephrine has been reported by Hartman (42). That epinephrine does increase the heat production has been attested by other authors (8, 43, 49, 50). Therefore it is only logical to conclude that the concomitant increase in heat production with the release of epineph-

rine is an important factor in slowing the rate of cooling.

This conclusion might be contested by some on the basis that a higher degree of anesthesia is required for those dogs upon which surgical procedures were to be performed. In the preparation of the animals for immersion, an attempt was made to eliminate such a variable by maintaining all animals at a minimal degree of anesthesia; therefore, if the animal appeared to be deeply anesthetized at the completion of the surgery, a certain amount of recovery was permitted before it was immersed in the water. The time required for such a recovery was never long because of the nature of the short acting barbiturate, sodium pentothal. Even if the surgery animals were more deeply anesthetized, the effect would be one of increasing the cooling rate by suppressing the shivering reflex (59). For these reasons, it would seem that the surgical operation and not the level of anesthesia was the factor which caused the variation in the rate of cooling found to exist.

The amount of hair coat was shown to have some influence upon the rate of cooling. The dogs with thick, heavy coats of hair do cool more slowly than those with short, light hair or without any hair at all. This would be expected since the heavy hair will form a dense mat over the body surface when it is wetted and will therefore form an insulating wall around the animal. The short hairs will not hold together sufficiently to form such an insulating wall and therefore little or no difference can be observed between short-haired and depilated dogs.

This finding of the effect of hair coat in cooling time is in contrast to that reported by Spealman (68) and Haterius and Maison (46)

wherein neither authors could show any effect of depilation in immersion type hypothermia. The aberrant results of these authors doubtless stem from the very limited number of observations reported.

Anesthetics have a profound effect upon the rate of cooling. Spealman (68) and Woodruff (77) found that certain dogs would not cool appreciably unless an anesthetic were administered. As to the comparison of the effects of the various anesthetics, little has been shown. Haterius and Maison (46) found no difference between cyclopropane and pentothal. In this work, a comparison was made between the rates of cooling under a volatile, respiratory anesthetic, ether, and a barbiturate, pentothal. No significant difference was found in the rate of cooling, but there was an indication that under ether the dogs might cool more slowly (P equals 0.10). A further study using more dogs under ether, might give a significant difference between the two techniques. The marked effect on the rate of cooling under the long acting barbiturates was shown in an experiment where sodium amytal was used on a dog which had been twice cooled under pentothal and it was found that the rate of cooling increased by 54% (59). This particular dog had shivered violently while under pentothal but did not shiver at all under sodium amytal.

An analysis of the difference in the rate of cooling between the sexes failed to demonstrate any significant difference.

An analysis of variance made between the three weight groups consisting of dogs weighing from 0 to 9.9 kilograms, from 10.0 to 14.9 kilograms, and from 15.0 and above, failed to show any significance.

The animals were grouped according to hair covering and whether or not surgery had been performed. This grouping lowered the number of dogs available for each analysis thereby increasing the severity of the statistical test. A statistical analysis of the combined means, i.e., the mean for all sub-groups of a particular weight classification, failed to demonstrate any significant difference between the rates of cooling. It should be noted that in each case, the mean rate of cooling for dogs weighing 15.0 kilograms and over was less than that for the smaller animals. Again it might be true that with carefully controlled data it would be found that the larger dogs do cool significantly slower than the smaller dogs.

The effect of shivering upon the rate of cooling is disputed. Haterius and Maison (46) have reported that they found shivering to have little or no effect upon the rate of cooling in a small series of trials. Nevertheless, it is interesting to note that Penrod (59) found one dog to shiver with such an intensity that it temporarily reversed the rate of cooling. In the study of the effect of shivering intensity on the rate of cooling, the breakdown of the animals into the various graded intensities and sub-groups left too few animals in any one particular classification for a good statistical test. For this reason the various sub-groups under each graded intensity were combined and the resultant mean rates of cooling were subjected to an analysis of variance wherein a significant difference was found to exist. It would seem that this difference was due to the varied intensity of shivering even though the combined mean rates of cooling are somewhat influenced by other factors

since an inspection of the data does not show a predominance of any one sub-group.

An inspection of the combined mean rates of cooling as presented in Table 4 shows an interesting deviation from the normal retardation of the rate of cooling with increasing shivering intensity for those animals shivering with an intensity of grade 1. It is seen that the mean rate of cooling increases from a value of 0.175° C./min. for those dogs that did not shiver at all to a value of 0.200° C./min. for those dogs that shivered minimally. Although this difference is not significant it is a marked one for such a large number of animals and might prove to be significant with an increased number of animals. This difference could be ascribed to two factors: first, the slight shivering would increase the movement of the water surrounding the animal and in so doing would increase the conductive heat loss, thus with a minimal amount of shivering the increase in conductive heat loss might predominate over the increase in heat production from the shiver; second, the shiver might stimulate peripheral blood flow to such an extent that the increased heat loss through this means could not be compensated by the minimal increase in heat production. The data do not warrant a complete explanation but do suggest that one or more of the above mentioned factors does exhibit a marked influence upon the rate of cooling when a minimal amount of shivering is instituted.

Penrod (59) compared the rates of cooling of several dogs to those of freshly sacrificed animals (0.181° C./min.) and found that the only dogs which cooled at a slower rate than the dead animals were those

which shivered considerably. The results herein reported would seem to substantiate this view. Aside from indicating that shivering does have an effect upon the rate of cooling, this comparison also indicated to him that the living animal is not capable of effecting a degree of peripheral vasoconstriction sufficient to prevent the loss of an amount of heat which is greater than that of a dead animal for the same time interval.

A study of viscosity changes in the hypothermic dog is in progress at this time, but sufficient data have not been accumulated to warrant a report. Indications are that the viscosity, or what may be more properly termed the rate of flow through a narrow glass capillary, increases above that to be expected from the actual physical cooling of the blood. This increase might be partially explained by a fluid loss to the tissues on cooling, but as yet it cannot be assured that this would serve as a complete explanation. A comparison of the increase to changes in hematocrit can determine whether or not the fluid loss to the tissue is the only factor causing the increase above the expected. The effect of any increase in the viscosity of the blood would in any case be one of slowing the rate of cooling by slowing the peripheral passage of blood with a resultant lowered heat loss.

SUMMARY

1. A study was made on the effects of thiouracil and thyroxin administration in rats subjected to immersion hypothermia. A statistical study was also made on the effects of various factors on the rate of cooling in dogs.

2. The thiouracil and thyroxin diets had no effect on the mortality of rats exposed to cold, but a statistically significant increase in the rate of cooling for rats fed a propylthiouracil diet was observed.

3. A daily dose of 4 mg. per kilogram of thyroxin had no effect on the oxygen consumption but a statistically significant increase in the rate of cooling of the dog was found.

4. It was found that heavily coated dogs cool more slowly than lightly coated or depilated dogs. No significant difference was found between the rates of cooling for short-haired and depilated dogs.

5. No significant difference was found between the rate of cooling of ether anesthetized dogs and of pentothal anesthetized dogs.

6. A high degree of significance was found to exist between the rate of cooling for dogs upon which surgical procedures had been performed and those upon which no surgery had been performed. The decrease in the rate of cooling of surgery dogs was postulated to be due to an increase in the flow of epinephrine.

7. No difference was found to exist between the rate of cooling of male and female dogs.

8. No difference was found in the rate of cooling between the weight groups 0 to 9.9, 10.0 to 14.9, and 15.0 kilograms and above, but

there was some indication that the heavier dogs cool more slowly than the lighter dogs.

9. Shivering was found to have a significant effect in slowing the rate of cooling. It was also observed that dogs exhibiting a minimal amount of shivering cool at a faster rate than dogs which do not shiver at all. Although no statistical significance can be demonstrated between the mean rates of cooling for the two groups, the difference does seem to be great enough to warrant some consideration.

BIBLIOGRAPHY

1. Adolph, E. F. Lethal limits of cold immersion in adult rats. Am. J. Physiol., 155: 378-387, 1948.

2. Ariel, I., Bishop, F. W., and Warren, S. L. Studies on the effect of hypothermia. I. Acute physical and physiological changes induced by the prolonged hypothermic state in the rabbit. Cancer Research, 3: 448-453, 1943.

3. Ariel, I. and Warren, S. L. Studies on the effect of hypothermia. II. The active role of the thyroid gland in hypothermic states in the rabbit. Cancer Research, 3: 454-463, 1943.

4. Barbour, H. G. The heat regulating mechanism of the body. Physiol. Rev., 1: 295-326, 1921.

5. Barbour, H. G., McKay, E. A., and Griffith, W. P. Water shifts in deep hypothermia. Am. J. Physiol., 140: 9-19, 1943-44.

6. Barcroft, H. and Edholm, O. G. The effect of temperature on blood flow and deep temperature in the human forearm. J. Physiol., 102: 5-20, 1943-44.

7. Blood, F. R., Glover, R. M., Henderson, J. B., and D'Amour, F. E. Relationship between hypoxia, oxygen consumption and body temperature. Am. J. Physiol., 156: 62-66, 1949.

8. Boothby, W. M. and Sandiford, I. The calorigenic action of adrenalin chlorid. Am. J. Physiol., 66: 93-123, 1923.

9. Britton, S. W. Studies on the conditions of activity in endocrine glands. XXII. Adrenin secretion on exposure to cold, together with a possible explanation of hibernation. Am. J. Physiol., 84: 119-131, 1928.

10. Britton, S. W. Extreme hypothermia in various animals and man. Canad. M. A. J., 22: 257-261, 1930.

11. Brobeck, J. R. Physiology of heat and cold. Ann. Rev. Physiol., 8: 65-88, 1946.

12. Burton, A. C. Temperature regulation. Ann. Rev. Physiol., 1: 109-130, 1939.

13. Burton, A. C. and Bronk, D. W. The motor mechanism of shivering and of thermal muscular tone. Am. J. Physiol., 119: 284, 1937.

14. Cannon, W. B., Querido, A., Britton, S. W., and Bright, E. M. Studies on conditions of activity in endocrine glands. XXI. The role of adrenal secretion in the chemical control of body temperature. Am. J. Physiol., 79: 466-507, 1926-27.

15. Cassidy, G. J., Dworkin, S., and Finney, W. H. The action of insulin on the domestic fowl. Am. J. Physiol., 75: 609-615, 1925-26.

16. Cassidy, G. J., Dworkin, S., and Finney, W. H. The effect of various sugars (and of adrenalin and pituitrin) in restoring the shivering reflex. Am. J. Physiol., 77: 211-218, 1926.

17. Cori, C. F. and Cori, G. T. The mechanism of epinephrine action. I. The influence of epinephrine on the carbohydrate metabolism of fasting rats, with a note on new formation of carbohydrates. J. Biol. Chem., 79: 309-319, 1928.

18. Cori, C. F. and Cori, G. T. The mechanism of epinephrine action. II. The influence of epinephrine and insulin on the carbohydrate metabolism of rats in the postabsorptive state. J. Biol. Chem., 79: 321-341, 1928.

19. Cori, C. F. and Cori, G. T. The mechanism of epinephrine action. III. The influence of epinephrine on the utilization of absorbed glucose. J. Biol. Chem., 79: 343-355, 1928.

20. Cramer, W. and Ludford, R. J. On cellular activity and cellular structure as studied in the thyroid gland. J. Physiol., 61: 398-408, 1926.

21. Crismon, J. M. Effect of hypothermia on the heart rate, the arterial pressure and the electrocardiogram of the rat. Arch. Int. Med., 74: 235-243, 1944.

22. Cushing, H. and Goetsch, E. Hibernation and the pituitary body. J. Exper. Med., 22: 25-47, 1915.

23. Day, R. The effect of cold on man. Josiah Macy Foundation Review Series Vol. I, No. 2, 1943.

24. Deighton, T. Physical factors in body temperature maintenance and heat elimination. Physiol. Rev., 13: 427-465, 1933.

25. Dempsey, E. W. and Astwood, E. B. Determination of the rate of thyroid hormone secretion at various environmental temperatures. Endocrinology, 32: 509-518, 1943.

26. DuBois, E. F. Heat loss from the human body. Bull. New York Acad. Med., 15: 143-173, 1939.

27. Eckstein, R. W., Book, D., and Gregg, D. E. Blood viscosity under different experimental conditions and its effect on blood flow. Am. J. Physiol., 135: 772-775, 1941-42.

28. Elliott, H. W. An analysis of the failure of respiration and circulation resulting from extreme hypothermia in the albino rat. Thesis. Stanford Univ. June 1946.

29. Fahraeus, R. and Lindquist, T. The viscosity of the blood in narrow capillary tubes. Am. J. Physiol., 96: 562-568, 1931.

30. Fairfield, J. Effects of cold on infant rats: body temperatures, oxygen consumption, electrocardiograms. Am. J. Physiol., 155: 355-365, 1948.

31. Finney, W. H., Dworkin, S., and Cassidy, G. J. The effects of lowered body temperature and of insulin on the respiratory quotients of dogs. Am. J. Physiol., 80: 301-310, 1927.

32. Fuhrman, F. A. and Crismon, J. M. The influence of acute hypothermia on the rate of oxygen consumption and glycogen content of the liver and on the blood glucose. Am. J. Physiol., 149: 552-560, 1947.

33. Gagge, A. P. and Herrington, L. P. Physiological effects of heat and cold. Ann. Rev. Physiol., 9: 409-428, 1947.

34. Gellhorn, E. Oxygen deficiency, carbon dioxide and temperature regulation. Am. J. Physiol., 120: 190-194, 1937.

35. Gellhorn, E. and Janus, A. The influence of partial pressure of O_2 on body temperature. Am. J. Physiol., 116: 327-329, 1936.

36. Gerard, R. W. and McIntyre, M. The effect of thyroid feeding on tissure respiration. Am. J. Physiol., 103: 225-231, 1936.

37. Grossman, M. S. and Penrod, K. E. The thyroid and high oxygen poisoning in rats. Am. J. Physiol., 156: 182-184, 1949.

38. Grossman, M. S. and Penrod, K. E. Relationship of hypothermia to high oxygen poisoning. Am. J. Physiol., 156: 177-181, 1949.

39. Hamilton, J. B. The effect of hypothermic states upon reflex and central nervous system activity. Yale J. Biol. and Med., 9: 327-332, 1937.

40. Hardy, J. D. and DuBois, E. F. Basal metabolism, radiation, convection and vaporization at temperatures of 22 to 35° C. J. Nutrition, 15: 477-497, 1938.

41. Hardy, J. D. and Goodell, H. Thermoregulatory phenomena associated with exposure to warm and cold envoronments. Federation Proc., 6: 122, 1947.

42. Hartman, F. A. Some conditions determining adrenal secretion. Am. J. Physiol., 63: 405, 1922-23.

43. Hartman, F. A. and Brownell, K. A. Response to chilling and recovery in adrenalectomized cats. Am. J. Physiol., 141: 651-661, 1944.

44. Hartman, F. A. and Hartman, W. B. Influence of temperature changes on the secretion of epinephrin. Am. J. Physiol,, 65: 612-622, 1923.

45. Hartman, F. A., McCordock, H. A., and Loder, M. M. Conditions determining adrenal secretion. Am. J. Physiol., 64: 1-34, 1923.

46. Haterius, H. O. and Maison, G. L. Experimental hypothermia and rewarming in the dog: recovery after severe reduction in body temperature. Am. J. Physiol., 152: 225-232, 1948.

47. Hemingway, A. The standardization of temperature regulatory responses of dogs to cold. Am. J. Physiol., 128: 736-746, 1939-40.

48. Hill, R. M. The control of body-temperature in white rats. Am. J. Physiol., 149: 650-656, 1947.

49. Horvath, S. M., Hitchcock, F. A., and Hartman, F. A. Response to cold after reduction of adrenal tissue. Am. J. Physiol., 121: 178-184, 1938.

50. Hunt, H. B. and Bright, E. M. Studies on the conditions of activity in endocrine glands. XVIII. Locus of the calorigenic action of adrenalin with observations on tissue metabolism. Am. J. Physiol., 77: 353-370, 1926.

51. Jung, R., Doupe, J., and Carmichael, E. A. Shivering; a clinical study of the influence of sensation. Brain, 60: 28-38, 1937.

52. Kenyon, A. T. The histological changes in the thyroid gland of the white rat exposed to cold. Am. J. Path., 9: 347-368, 1933.

53. Kottke, F. J., Phalen, J. S., and Visscher, M. B. An effect of breathing high oxygen mixtures on shivering in man. Federation Proc., 3: 26, 1944.

54. Kottke, F. J., Phalen, J. S., and Visscher, M. B. Effect of breathing high oxygen mixtures on human metabolism during shivering. Federation Proc., 3: 26, 1944.

55. Leblond, C. P. and Gross, J. Factors modifying the response of thyroidectomized rats to low temperature. Anat. Rec., 84: 489, 1942.

56. Leblond, C. P., Gross, J., Peacock, W., and Evans, R. D. Metabolism of radio-iodine in the thyroids of rats exposed to high or low temperatures. Am. J. Physiol., 140: 671-676, 1943-44.

57. Mann, F. C. The ductless glands and hibernation. Am. J. Physiol., 41: 173-188, 1916.

58. Mills, C. A. Effects of external temperature, morphine, quinine and strychnine on thyroid activity. Am. J. Physiol., 46: 329-339, 1918.

59. Penrod, K. E. Oxygen consumption and cooling rates in immersion hypothermia in the dog. Am. J. Physiol., 157: 436-444, 1949.

60. Perkins, J. F., Jr., Li, M. C., Hoffman, F., and Hoffman, E. Sudden vasoconstriction in devervated or sympathectomized paws exposed to cold. Am. J. Physiol., 155: 165-178, 1948.

61. Rasmussen, A. T. The hypophysis cerebri of the woodchuck (Marmota Monax) with special reference to hibernation and inanition. Endocrinology, 5: 33-66, 1921.

62. Richards, R. L. The Peripheral Circulation in Health and Disease. Baltimore: Williams and Wilkins Co., 1946.

63. Ring, G. C. Thyroid stimulation by cold. Am. J. Physiol., 125: 244-250, 1939.

64. Scott, J. C. and Bazett, H. C. Temperature regulation. Ann. Rev. Physiol., 3: 107-130, 1941.

65. Spealman, C. R. Temperature and blood flow in extremities immersed in water. Proc. Soc. Exper. Biol. & Med., 56: 38-40, 1944.

66. Spealman, C. R. A characteristic of human temperature regulation. Proc. Soc. Exper. Biol. & Med., 60: 11-12, 1945.

67. Spealman, C. R. Body cooling of rats, rabbits and dogs following immersion in water, with a few observations on man. Am. J. Physiol., 146: 262-266, 1946.

68. Starr, P. and Roskelley, R. A comparison of the effects of cold and thyrotropic hormone on the thyroid gland. Am. J. Physiol., 130: 549-556, 1940.

69. Swift, R. W. The effects of low environmental temperature upon metabolism. J. Nutrition, 5: 213-225, 1932.

70. Swift, R. W. The effects of low environmental temperature upon metabolism. Am. J. Physiol., 97: 565, 1931.

71. Talbott, J. H. The physiologic and therapeutic effects of hypothermia. New England J. Med., 224: 281-288, 1941.

72. Tyslowitz, R. and Astwood, E. B. The influence of the pituitary and adrenal cortex on resistance to low environmental temperatures. Am. J. Physiol., 136: 22-31, 1942.

73. Uotila, U. U. The role of the cervical sympathetics in the regulation of thyroid and thyrotropic function. Endocrinology, 25: 63-70, 1939.

74. Uprus, V., Gaylor, J. B., and Carmichael, E. A. Shivering: a clinical study with especial references to the afferent and efferent pathways. Brain, 58: 220-232, 1935.

75. Wolff, O. and Greep, R. Histological study of thyroid gland of hypophysectomized rats exposed to cold. Proc. Soc. Exper. Biol. & Med., 36: 856-860, 1937.

76. Woodruff, L. M. Survival of hypothermia by the dog. Anesthesiology, 2: 410-420, 1941.

77. Zarrow, M. X. and Money, W. L. Involution of the adrenal cortex of rats treated with thiouracil. Endocrinology, 44: 345-358, 1949.

ABSTRACT

A presentation of the factors which effect the rate of cooling in immersion hypothermia for certain laboratory animals is made in this thesis. A review of the literature has been made and those physical, physiological, chemical and other factors which have been presumed to show an effect upon the cooling rate are discussed.

The experimental work performed in preparation for this presentation was aimed toward a study of the effect of the following on rate of cooling: hair coat, thyroxin, surgery, anesthetic, shivering, sex, and body size.

Due to the complex nature of the study proposed in this thesis, it was necessary to make concurrent observations on 94 dogs, all of which were cooled in an ice bath of 2-4° C. Certain variations were made in the preparation of the animals but they were all given a sedative dose of pentothal sodium prior to their immersion or preparation for immersion. In the analysis of the data, the 94 animals were divided into groups and sub-groups dependent upon their preparation with or without surgery, upon the hair covering, body weight, shivering intensity, sex, and type of anesthetic.

Of greatest interest was the finding that surgical procedures do significantly retard the rate of cooling. The statistical study was made on 46 dogs upon which surgical procedures had been performed and 31 dogs upon which no surgery had been performed. The mean cooling rates varied from 0.140° C./min. for the surgery dogs to 0.197° C./min.

for the non-surgery dogs, the difference proving to be highly significant (P is less than 0.001). The difference was explained upon the basis of an epinephrine release concurrent with the surgical operations.

Five arbitrary grades of shivering intensity are described in the thesis and a statistical analysis of the mean cooling rates for the dogs falling under each classification was made. Since the breakdown of the animals into the smaller sub-groups decreased the number of dogs for each test, a combined mean for all dogs under a particular shivering intensity was computed. A statistically significant difference was found to exist between the mean rates of cooling, the trend being one of a decreasing rate of cooling with increased shivering. An aberrant mean rate of cooling was found for those animals demonstrating a minimal amount of shivering, wherein the mean rate of cooling increased over that of the animals which did not shiver at all. The difference was not statistically significant but was marked. A possible explanation for the deviation has been offered in the thesis.

A statistical study made for the effect of hair coat showed significance between the rates of cooling for long-haired and short-haired dogs, but no significance between short-haired and depilated dogs. The results are such as would be expected since the heavy, long hair will mat down when wet and in so doing forms a protective insulated layer around the body surface. The short hair, on the otherhand, will not mat to any great extent and has a very limited effect in retarding the rate of cooling.

A thyroid study was made on two series of rats. Each series of

rats was broken down into three groups each of which was maintained on a specific diet. Two of the groups were made hypothyroid by a 6-n-propylthiouracil diet, two made hyperthyroid by a thyroxin diet while the remaining two groups were fed a normal diet and were used as controls.

It was found that the hypothyroid rats cooled significantly faster than either the control or hyperthyroid animals, but no significance could be found in the relative survivals when the animals were revived in room air from a depressed rectal temperature of 16.0° C. in one series and 15.0° C. in the other series. A high, but not statistically significant positive correlation (0.94) was found to exist between the metabolic state and the rate of cooling in the first series, while a positive correlation of only 0.45 was found in the second series, being far from the level of significance due to the increased rate of cooling of the hyperthyroid rats over that of the controls.

A thyroid study was also made on six dogs. After two immersions, the dogs were fed a special diet containing 4 mg. thyroxin per kilogram body weight for 13 days and were then cooled once again. No appreciable change in the oxygen consumption was observed for this thyroxin dose, but the rate of cooling did increase significantly. Oxygen consumptions were determined using a closed circuit respirometer and rectal temperatures were recorded on a constant recording Leeds Northrup Speedomax from a thermocouple inserted four inches into the rectum, this being the method for recording temperatures in all of the experiments on dogs.

If the dogs are divided into the three weight sub-groups, 0 to 9.9, 10.0 to 14.9, and 15.0 kilograms and above, the number of animals

available for a statistical test is too small for a good test so the groups were combined and an analysis of variance made on the combined means failed to show any significant difference between the rates of cooling. It was noted, however, that in most cases the larger animals, i.e., those over 15.0 kilograms, did cool more slowly than the others.

A comparison of the rates of cooling under ether anesthetic and under pentothal anesthetic failed to show a significant difference between the two in a very limited series. Although the rate of cooling under ether anesthetic was appreciably less than that under pentothal, it might be true that a significant difference was not found because of the relatively small number of ether dogs (8) studied.

A short discussion of the effect of blood viscosity changes is presented, but no data have been reported. The effect of the increased viscosity found toexist concurrent with a fall in rectal temperature would be to slow the rate of cooling.

A summary of the more important findings from the experimental work is presented in conclusion of the thesis.

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